Remarks

The new claims place the application in a condition for allowance or better position for appeal.

Support for the new claim 130 can be found, *inter alia*, on page 17, lines 31to 33 in the definition of vial. Retaining the solution in a sterile state indicates that the vial is sealed. Support for new claims 129 to 131 can be found, *inter alia*, on page 38, line 23 to 30, which clearly describes products having a single vial containing a solution or dual vials for the lyophilized formulation that is reconstituted by the patient.

Applicants respectfully request entry of the amendments. Differentiating the solution and reconstituted lyophilized formulations of the present invention better position the claims for allowance or appeal.

The Pending Rejection

Claim 128 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Keene et al., The Journal of Biological Chemistry 264(9): 4769-75 (1989) (*Keene*) in view of Skrabanja et al., EP 0853 945 A1 (*Skrabanja*) and Andya et al. US Patent No. 6,267,958 B1 (*Andya*).

All other rejections have been withdrawn.

The Problem Solved by the Claimed Invention

For over 30 years prior to the effective filing date of the instant application, products comprising FSH had been commercially sold. These products consisted of lyophilized formulations that had to be reconstituted with each use. That is, each time the patient needed treatment, the patient reconstituted a quantity of FSH with sterile water, measured out the desired dose in a syringe, immediately administered the reconstituted FSH by a subcutaneous injection, and discarded any unused material. This typically occurred one to three times per day, over a course of 10-14 days. Such a treatment regiment resulted in a significant loss of material, risked variability due to incomplete mixing during reconstitution, and was quite inconvenient for the patient. Unquestionably, there was a long-felt need in the art for alternative formulations of FSH and, in particular, a solution formulation that avoided reconstitution altogether or a

multi-use formulation that could be reconstituted once and then used over the course of therapy.

The present invention provides formulations of human FSH and benzyl alcohol in an aqueous diluent. The invention enables solution formulations of FSH and multi-use reconstituted FSH formulations. The invention, therefore, marks an improvement over decades old prior formulations of FSH.

The Prior Art Fails to Render the Claims Obvious

Others in the field were working toward solving the problems associated with lyophilized preparations of FSH. As noted in *Skrabanja*, cited by the Examiner:

> *The stability of proteins in aqueous formulations is generally a problem in pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions. Usually therefore those preparations are stored in a dry form, as is obtained after lyophilization. A stabilized gonadotropin containing lyophilized pharmaceutical formulation is disclosed in European Patent No. 448,146 (Akzo N V.) These preparations contain organic carboxylic acids, particularly citric acid, and optionally a non-reducing sugar such as sucrose. Another solid gonadotropin containing pharmaceutical composition comprising sucrose as a stabilizer is disclosed in the International Patent Application WO 93/11788 (Applied Research Systems ARS Holding NV.).*
>
> *Although these freeze-dried preparations are stable enough to guarantee sufficient shelf-lifes, they have the disadvantage that prior to administration reconstitution is necessary. The patient therefore necessarily has to reconstitute the dried glycoprotein in a solvent before use, which is a disadvantage and an inconvenience to the patient. In addition, the solvent must be provided together with the freeze-dried preparation of the gonadotropin.*
>
> *For a patient, who needs injections of a gonadotropin at regular times, for instance a patient receiving a daily dose of recFSH for ovulation induction, it would be of importance that the gonadotropin formulation is easy to handle, to dose and to inject. The reconstitution of a freeze-dried gonadotropin preparation demands prudence and carefulness and should be avoided it possible. It would facilitate the use of gonadotropins, if these glycoproteins could be produced and distributed as a stable solution to the patient, who could inject the medicament directly without reconstitution. In addition, a freeze-drying process is a*

costly and time consuming process step, and it would be an advantage if this step could be avoided when preparing a gonadotropin formulation.

A need exists therefore in a ready-for-use injection preparation, having a sufficient stability to guarantee a reasonable shelf-life.

Skabanja, page 2, line 42 to page 3, line 5.

Skrabanja's objective was clear – avoid reconstitution by preparing a ready-to-use solution by formulating the gonadotropin with a stabilizing amount of a polycarboxylic acid or a salt thereof and a thioether compound. The teaching of *Skrabanja* is comprehensive, leaving little doubt to the excipients contemplated and disclosed. The specification describes the claimed excipients (the carboxylic acids and thioether compounds), optional excipients (non-reducing sugars such as sucrose or trehalose and non-ionic surfactants) and is complete in its teaching. For example, page 4, lines 23 through 33, *Skrabanja* sets out nonionic surfactants such as Polysorbate 20, Polysorbate 80, Brij 35, or Pluronic F123 as an optional and preferred embodiment. Also on page 4, lines 46 to 48, specifies the water to be used and even notes that a water miscible solvent may be present as a co-solvent. The examples of *Skrabanja* are similarly complete, specifying the identity and amount of each and every excipient, even including the amount of water. *Skrabanja* is so complete in its teaching that the reference lacks the necessary suggestion or motivation to add an unnamed excipient. Furthermore, because *Skrabanja* expressly sought to avoid lyophilized formulations, it is incongruous to combine Skrabanja with the teaching of *Andya*, which is directed to lyophilized formulations of proteins. Thus, the starting point of the Examiner's rejection, that one skilled in the art would be motivated to combine *Skrabanja* with the lyophilized formulations of *Andya* lacks foundation and is plainly hindsight.

As noted by the Examiner, *Skrabanja* on page 5, lines 37 to 44, refers to use of a gonadotropin in cartridge and a injection device such as a pen-injector. At line 41, *Skrabanja* notes the "medicament can be in the form of a cartridge for multiple use." Specific reference is also made to the B-D pen injector. This passage, however, must be read in context of the patent and the state of the art. Only by impermissible hindsight does one reach an interpretation that this passage provides motivation to add an additional, unnamed excipient to the otherwise complete description of the disclosed

formulations. Likewise, only in hindsight, does one reach an interpretation to add a preservative, or benzyl alcohol in particular, to a solution formulation of FSH.

First, the passage is not specific to any particular gonadotropin. The gonadotropin, human chorionic gonadotropin (hCG), had been formulated with benzyl alcohol for multiple use since the 1950s; yet, for over 30 years, FSH had not been. Furthermore, the FSH heterodimer was recognized as being particularly susceptible to instability (*see* paragraphs 69 through 72 of the Declaration of Dr. Beals, and Ryan et al., *Recent Progr. Hormone Res.* 26:105-137 (1970); Strickland and Puett, *Biol. Chem.* 257:2954-2960 (1982); Reichert and Ramsey, *J. Biol. Chem.* 250:3034-3040 (1975)). A general reference to improved solution formulations having a polycarboxylic acid and a thioether would not dispel these stability and compatibility concerns, nor the prejudice that existed against exposing FSH to a preservative. Therefore, a general reference to "gonadotropins" in "a cartridge for multiple use" cannot be properly read to provide the requisite suggestion or motivation to prepare preserved, multiple use solution formulations of FSH and benzyl alcohol.

Second, the reference to "a cartridge for multiple use" follows a detailed and complete description of the formulations disclosed in *Skrabanja*. As noted, required, optional and preferred excipients are listed. These include sucrose or trehalose and non-ionic surfactants such as Polysorbate 20, Polysorbate 80, Brij 35, Pluronic F123 and even the option of water miscible solvents in the diluent. In view of such a description, and the ***complete absence*** of any description of any additional unnamed excipients and any discussion of preservative, the passage cited by the Examiner fails to provide the requisite suggestion or motivation to combine its teaching with *Andya* or to provide the necessary expectation of success. *See* Declaration of Dr. DeFelippis (filed with the current response), paragraphs 11-14 and 17-18.

The cited passage must also be read in the context of the art. Reference to "cartridges for multiple use" could have any number of meanings. For example, according to the "Note for Guidance on Maximum Shelf-life for Sterile Products for Human Use After First Opening or Following Reconstitution," an unpreserved, sterile product may be used multiple times so long as the in-use stability has been established. *See* EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS, COMMITTEE

FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP), Guidance CPMP/QWP/159/96, 1999. Typically, the unpreserved product would not be used for more than 24 hours when stored at 2-8°C, unless reconstitution or dilution occurred under controlled and validated aseptic conditions. *Id.* Within this 24-hour period, a formulation may be administered multiple times, thus making it "multiple use." This interpretation is consistent with Skrabanja's complete silence on preservatives.

Another possible meaning is that "cartridges for multiple use" refers to use in the clinical setting. To avoid complications with reconstitution, patients using FSH often visited a clinic or hospital to receive their injections. The clinic reconstituted the lyophilized FSH and administered the product to the patient, changing needles between patients. For example, with larger vials or cartridges such as the 300 IU package, the physician could deliver a typical 150 IU dose to two patients (i.e., multiple use) rather than just one, and avoid discarding the expensive product.

Moreover, the dose of FSH to be delivered to the patient is variable, depending on the needs of the patient. The patient titrates the dose and could administer more than one injection for any given dose. The pen injector would provide a means to vary the dose and to administer these variable doses. Thus, the reference to "cartridges for multiple use" would also be a reference to using the same cartridge to administer a variety of doses. As can be seen, this passage cited by the Examiner simply lacks the clarity and specificity to provide any suggestion or expectation of success.

Andya is also cited by the Examiner as providing the "motivation and the expectation of success." *Andya*, like *Skrabanja*, simply fails in this regard and does not provide the necessary motivation to combine with Skrabanja and Keene or any expectation of success. *Andya* generally describes lyophilized formulations of a multitude of protein formulations. The solution formulations of the present invention (new Claims 129 and 130) sought to overcome problems associated with lyophilized protein formulations. The multi-use reconstituted formulation sought to minimize these problems by allowing the solution to be stored for an extended period.

Andya requires a very high protein concentration (≥50 mg protein/mL diluent). In contrast, the instant invention only requires a concentration of 5.0 μg/mL to 2 mg/mL. As noted by Dr. DeFelippis, the protein concentrations in Andya are at least 25 times

more concentrated, and could be much more concentrated. Declaration of Dr. DeFelippis, paragraph 21. Relatively dilute solutions of FSH were known to be conformationally unstable (Skrabanja, page 2, 42-45). Thus, the extremely high concentrated protein solution described in *Andya* is not predictive or suggestive of stability of an FSH solution with a much lower concentration. Declaration of Dr. DeFelippis, paragraph 21.

Andya also describes an improvement – the addition of certain excipients, namely lyoprotectant such as sucrose or trehalose such that the lyophilized protein formulations are stable upon storage. The formulations are stable as a solid, freeze-dried powder. *Andya* also notes that upon reconstitution the formulation is stable "for at least the time over which it will be administered to a patient." *Andya,* column 1, lines 55 to 59. Thus, *Andya* describes certain lyoprotectants that provide stability to freeze dried protein formulations but also teaches to limit the use of the reconstituted protein to the period of time over which the protein is administered to the patient (a period generally shorter than the shelf-life required to manufacture, distribute, store, and finally administer a solution).

Significantly, a preservative is an **optional** excipient in the diluent used for reconstitution (*Andya*, column 17, line 29 to 37). The term "preservative" is exemplified on column 9, line 46 to 58 of *Andya*:

> *Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl and benzyl alcohol, allyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol. The most preferred preservative herein is benzyl alcohol.*

The reason benzyl alcohol is identified as preferred is unstated. *Andya* does not describe any stability effects of the preservative and later notes that "*[t]he amount of preservative is determined by assessing different preservative concentrations for compatibility with the protein and preservative efficacy testing*." *Andya*, Column 17, lines 32 to 34. This hardly provides the motivation or suggestion for anything, let alone combining the present invention with *Skrabanja*. In fact, by lyophilizing the formulation and only including the preservative as an ***optional*** ingredient, *Andya* could be read to reasonably

suggest the opposite -- that solutions of the proteins are not sufficiently stable to avoid lyophilization and the problems of freeze-dried formulations.

Andya also describes a plethora of proteins. *Andya* notes that "protein" means:

> *[A] sequence of amino acids for which the chain length is sufficient to produce the higher levels of tertiary and/or quaternary structure. This is to distinguish from "peptides" or other small molecular weight drugs that do not have such structure. Typically, the protein herein will have a molecular weight of at least about 15-20 kD, preferably at least about 20 kD.*
>
> *Examples of proteins encompassed within the definition herein include mammalian proteins, such as, e.g, growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; α-1 - antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIIIC, factor , tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or tissue-type plasminogen activator (t-PA); bombazine; thrombin; tumor necrosis factor-α and -β; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-α); serum albumin such as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; DNase; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; an integrin; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-α and TGF-β, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I); insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19 and CD20; erythropoietin (EPO); thrombopoietin (TPO); osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-α, -β, and -.gamma.; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1 to IL-10; superoxide dismutase; T-ell receptors; surface membrane proteins; decay accelerating factor (DAF); a viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; immunoadhesins; antibodies; and biologically active fragments or variants of any of the above listed polypeptides.*

Andya Column 6, line 37 through Column 7, line 17.

One skilled in the art would readily recognize that some of these proteins would not be compatible with benzyl alcohol. *See* Declaration of Dr. DeFelippis, paragraph 13 and 19. As noted in the accompanying Declaration of Dr. DeFelippis, protein-preservative interactions are unique and largely unpredictable. The art demonstrates that some of the proteins listed in *Andya* are not compatible with benzyl alcohol. For example, interferon γ, which is listed amongst the plethora of proteins (column 7, line 9), was known to be unstable with benzyl alcohol. Lam *et al.*, *Pharm. Res.* 14(6):725-29 (1997). Similarly, interleukin 1-R, also listed in *Andya* (column 7, line 10), was known to be unstable with benzyl alcohol. Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998). And, insulin-like growth factor 1 was known to be unstable with benzyl alcohol in Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997). As noted in Akers, Michael J., *J. Pharm. Sci* 81(11): 2294 bottom of the right hand column:

> *Any formulator of a protein or peptide dosage form likely has experienced compatibility problems in attempting to develop multi-dose biopharmaceutical products. However, very few articles have been published describing these problems.*

In the case of FSH, doubt also existed whether a preserved formulation was possible. "There is substantial evidence in the literature indicating that heterodimers can dissociate under physiological or acidic conditions (Ryan *et al.*, *Recent Progr. Hormone Res.* 26:105-137 (1970); Strickland and Puett, *Biol. Chem.* 257:2954-2960 (1982); Reichert and Ramsey, *J. Biol. Chem.* 250:3034-3040 (1975))", and since "[t]he alpha and beta subunits [of FSH] bind non-covalently .... , the binding was thought to be more susceptible to protein destabilization agents" *(see* the instant application page 3, lines 14-16).

Therefore, *Andya*'s reference to benzyl alcohol as a "preferred" and "exemplary" embodiment must be read in context. While *Andya* broadly describes an innumerable number of proteins, only two antibodies, Anti-Her2 and Anti-IgE, are described in any detail and exemplified. For these exemplified antibodies, benzyl alcohol is used in the diluent for reconstitution. For these given proteins, *Andya* would be understood as identifying benzyl alcohol as the preferred preservative. *See* Declaration of Dr. DeFelippis, paragraph 19. It is noteworthy that *Andya* reads, "The most preferred preservative herein is benzyl alcohol." Column 9, line 58. Given the expansive list of

proteins, the known incapability of some of the listed proteins with benzyl alcohol, and the known unpredictability of protein-preservative interactions, the "herein" would direct the reader and be understood as referring merely to Anti-Her2 and Anti-IgE.

As noted by Dr. DeFelippis, *Andya* would **not** be interpreted as a suggestion or motivation to use a preservative, or particularly benzyl alcohol, in a solution formulation of each of the innumerable number of proteins included in the definition or the hundreds of proteins explicitly listed, including FSH. *See* Declaration of Dr. DeFelippis, paragraph 19 and 20. The unpredictability of protein-preservative compatibility and the known incompatibility of some of the proteins listed with benzyl alcohol precludes any such sweeping generalization from providing the required suggestion to combine *Andya* with *Skrabanja* or the requisite expectation of success. Thus, *Andya* also fails to support the Examiner's rejection.

Plainly, the Examiner is picking and choosing the prior art with the benefit of hindsight. Such practice has been admonished by the Federal Circuit. The Court noted in McGinley v. Franklin Sports Inc., 60 USPQ2d 1001 (CA FC 2001):

> The genius of invention is often a combination of known elements which in hindsight seems preordained. To prevent hindsight invalidation of patent claims, the law requires some "teaching, suggestion or reason" to combine cited references. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579, 42 U.S.P.Q.2d 1378, 1383(Fed. Cir. 1997). When the art in question is relatively simple, as is the case here, the opportunity to judge by hindsight is particularly tempting. Consequently, the tests of whether to combine references need to be applied rigorously. [citations omitted]

In addition to the use of preservative in *Andya*, the Examiner seeks to justify the combination of references stating:

> This suggestion or motivation can be found in the prior art references themselves, *in the knowledge generally available to one skilled in the art* or, in some cases, from the nature of the problem to be solved. The addition of preservatives to pharmaceutical formulations is deemed routine and well within the purview of the skilled artisan. Furthermore, Andya teaches the use of various preservatives in FSH pharmaceutical formulations.

Emphasis in the original, Final Action dated March 18, 2004, page 7.

For the reasons already noted, *Skrabanja* and *Andya* fail to provide the suggestion, motivation, or expectation of success. The Examiner's unsupported reference

to "knowledge generally available" simply ignores the noted instability of FSH in the prior art, the long-felt need to improve FSH formulations, and the prior attempts to stabilize FSH (*see* Moyle *et al.*, U.S. Pat. No. 5,508,261 (reference AB on Applicants' Information Disclosure Form 1449), which sought to improve the stability of FSH through preparation of analogs, Boime *et al.*, U.S. Pat. No. 6,638,890 (reference AU), which sought to improve stability by preparing single-chain monomers of glycoproteins, as opposed to non-covalently bonded heterodimers, and Skrabanja *et al.*, *supra*, which sought to improve stability by adding a thioether (i.e., methionine)). Such unsupported justification is exactly the hindsight that the Federal Circuit admonished in McGinley. Only in hindsight does one skilled in the art pick and choose FSH from the long list of proteins described in *Andya* with the gonadotropins identified in *Skrabanja* and then pick and choose benzyl alcohol from known preservatives listed in *Andya*. And, even if one were to pick and choose FSH and benzyl alcohol, the inherent unpredictability in formulation chemistry does not provide the required expectation of success. As noted in REMINGTON'S PHARMACEUTICAL SCIENCES 1550 (Gennaro et al. eds., 1990), *"Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another."*

Protein-preservative compatibility is recognized as being unpredictable. Declaration of Dr. DeFelippis, paragraphs 11 to 14. FSH, a complex heterodimer, was recognized as being susceptible to protein instability due to potential disruption in the noncovalent interactions that form the quaternary structure. *Id.* The perceived instability of the FSH heterodimer in the presence of a preservative was reinforced by the fact that FSH had been sold only in lyophilized forms and only for single use for over 30 years. Declaration of Dr. Beals (filed February 18, 2003), paragraph 41. Thus, when read in context, neither *Skrabanja*, nor *Andya*, nor the general knowledge in the art provide any expectation of success. Accordingly, the Examiner's *prima facie* finding of obviousness is improper.

Rebuttal Evidence

The Examiner did not comment in the Final Office Action on certain rebuttal evidence that applicants had previously submitted. Thus, the Examiner has apparently failed to consider all evidence on the question of obviousness. In re Piasecki, 223 USPQ 785, 787 (Fed. Cir. 1984) ("All evidence on the question of obviousness must be considered, both that supporting and that rebutting the prima facie case."). Applicants respectfully request that the Examiner reconsider all evidence of record, including the declarations submitted by Dr. Beals and Dr. Wijayaratne. Applicants assert that when all the evidence of record is properly weighed and evaluated, the presently claimed invention must be concluded to be un-obvious.

The Declaration of Dr. Beals established the recognized instability of FSH (*See* paragraphs 69 through 72) and demonstrated a long-felt need for improved formulations of FSH (*See* paragraphs 41, 68 and 72 through 77). The declaration further notes that other gonadotropins, namely hCG, were formulated as preserved solutions with benzyl alcohol. Dr. Beals further established that, despite the fact that the nature of the usage of FSH products (daily treatment, over a period of about 10-14 days, with the need for typically 1 –3 injections per day) made them ideally suited for multi-dose and despite the fact the means to create a multi-dose product were generally known, no p multi-dose FSH products were known. The fact that a seemingly simple invention was at the fingertips of skilled artisans in the field, yet not discovered, is **powerful, contemporaneous evidence of non-obviousness.**

Applicants feel compelled to point out an apparent misunderstanding by the Examiner in evaluating Dr. Beals' declaration. The Examiner noted at page 8 of the Office Action dated April 16, 2003:

> *"Furthermore, sucrose, sodium citrate, lactose, polysorbate 20 and phosphate salts, which Beals cites above, are all considered preservatives. Skrabanja et al., EP 0853 945 Al, teaches stable preserved liquid FSH comprising preservatives (sucrose) in a multi-dose pharmaceutical product."*

Discounting Dr. Beal's evidence on this basis is factually incorrect. Sucrose, sodium citrate, lactose, polysorbate 20 and phosphate salts are plainly not preservatives as the term is used in the present invention nor as the terms are used in the art. Sucrose is identified as a nonreducing disaccharide (*see Skrabanja*, page 4, line 16; also referred to

as a "lyoprotectant" in Akers, *J. Pharm. Sci.* 91(11):2283-2300, 2285 (2002)); sodium citrate is identified as a stabilizer (*see Skrabanja*, page 4, line 12; Akers, *J. Pharm. Sci.* 91(11):2283-2300, 2285 (2002)); polysorbate 20 is identified as a nonionic surfactant (*see Skrabanja*, page 4, line 28; also referred to as the "surface-active agent" "polyoxyethylene sorbitan monolaurate (Tween 20)" in Akers, *J. Pharm. Sci.* 91(11):2283-2300, 2285 (2002)); and phosphate salts are recognized as buffers (*see*, for example, Akers, *J. Pharm. Sci.* 91(11):2283-2300, 2288 (2002) and REMINGTON'S PHARMACEUTICAL SCIENCES p. 1550, "Buffers" (Gennaro et al. eds., 1990)).

Applicants therefore respectfully request that the Examiner review the evidence provided by Dr. Beals with respect to the recognized instability of FSH and the long-standing but unmet need for the present invention.

In rejecting of Dr. Wijayaratne in the Office Action of April 16, 2003, the Examiner stated:

> *The declarations do not demonstrate an unexpected property because benzyl alcohol is known in the art as a preservative. The claimed invention does not have significance equal to or greater than the expected properties. There are no unexpected beneficial results. The stability results of FSH and benzyl alcohol were not significantly advantageous compared to the control (FSH alone).*

Office Action dated April 16, 2003 page 7 bridging to page 8.

Applicants believe that the Examiner misapprehended the import of Dr. Wijayaratne's declaration. Dr. Wijayarante's declaration provides evidence that stability can be achieved where such stability was reasonably expected to be unachievable. This was unexpected, as Dr. Wijayaratne states. In view of such evidence, the Examiner's disregard of the declaration is improper. Such data support a finding of unobviousness.

Commercial success

There can be no question that the use of benzyl alcohol has contributed to the commercial success of two products now commercially sold, PUREGON® brand FSH and GONAL-F® MULTI-DOSE brand FSH. Both products comprise human FSH and benzyl alcohol in an aqueous diluent, wherein

(a) the concentration of FSH is 5.0 μg/mL to 2 mg/mL,

(b) the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions, and
(c) the formulation is suitable for multi-dose administration by injection.

Such products were introduced into the market in 2000 and 2001. Since introduction, GONAL-F® MULTI-DOSE brand FSH has garnered 15.7% of the US market, 25.2 % of the Canadian market and an average of 18.8% of the European market (ranging from 1.2% to 37.6%) by Q4-2002. PUREGON® has garnered 24.2% of the Canadian market and an average of 23.9% of the Europe market (ranging from 2.8% to 53.9%) in Q42002 (The US product, Follistim®-AQ was approved in 2004, and thus, US data are not available).

A review of Serono's website (http://www.seronofertility.com/to_ht_gonalF.jsp) makes clear that the success of GONAL-F® MULTI-DOSE is attributable at least in part to the use of benzyl alcohol thereby making the reconstituted formulation suitable for multi-dose administration. For example, the website provides:

"Gonal-f® is the most prescribed FSH in the US and in the world. It is the only FSH available in convenient multi-dose vials, offering several important benefits to patients:

Fewer Steps Gonal-f® Multi-Dose comes with a pre-filled diluent syringe, eliminating the extra step of preparing a diluent syringe.

Less Mixing Each Gonal-f® Multi-Dose vial contains as much medicine as 14 single dose vials or ampules of 75 IU each, so you only have to mix one time to have treatment prepared over several days. After reconstitution, the solution must be refrigerated.

Patient-Preferred
In a recent study, 96% of patients said Gonal-f® Multi-Dose was easy to handle, and 94% preferred the convenience of one-step reconstitution.[1]...

[1] Hinrichsen MJ, Weise G. German Phase III open multicenter study to evaluate the convenience and safety of recombinant FSH injections supplied as 1200 IU multidose (Gonal-f® Multi-Dose) in ART cycles. ESHRE, June 2002."

With GONAL-F® brand FSH, FSH is sold as a lyophilized product and reconstituted in a diluent comprising benzyl alcohol so that the solution can be used over the course of therapy (up to 28 days).

PUREGON® is a solution product comprising FSH and benzyl alcohol. With regard to PUREGON®, which is now approved in the US as FOLLISTIM®, Organon, the manufacturer, stated:

> The U.S. Food and Drug Administration (FDA) today announced approval of Follistim®-AQ TM cartridge (follitropin beta injection) in the United States. Follistim-AQ cartridge is the first follicle stimulating hormone (FSH) treatment available in a pre-filled, pre-mixed solution, eliminating the need for patients to mix one or more vials of medication. Follistim-AQ cartridge is designed to be used only with the Follistim Pen®, an innovative pen device that facilitates accurate delivery of individualized doses of pre-mixed follitropin beta injection, a highly effective and widely used prescription fertility medication. Follistim is prescribed for women undergoing assisted reproductive treatments (ART) such as in vitro fertilization (IVF), and for the induction of ovulation to achieve pregnancy. Follistim-AQ cartridge, used with the Follistim Pen, provides women with a discreet, convenient method to self-administer fertility treatment with ease and confidence using the unique dial-a-dose feature. Organon USA Inc. markets Follistim-AQ cartridge and Follistim Pen. In Europe it is marketed under the brand name PUREGON Pen®.

24 March 2004 *(Arnhem, The Netherlands).* Although not explicit in the press release, Follistim-AQ is a solution comprising FSH and benzyl alcohol so that the solution can be used over the course of therapy.

The commercial success of these products provides further evidence that the present invention provided a significant and nonobvious advance over the art and is therefore patentable.

Summary

Applicants have presented compelling evidence demonstrating:

(1) The clear disadvantages of a lyophilized protein product and the treatment regiment of FSH created a need to discover improved formulations of FSH (Declaration of Dr. Beals, paragraph 72);

(2) FSH is a complex heterodimer and had been formulated as a lyophilized, single use product for over 30 years (Declaration of Dr. Beals, paragraph 41);

(3) As a complex heterodimer, FSH was characterized in the art as being susceptible to protein instability (Declarations of Dr. Beals, paragraphs 69-71, and DeFelippis, paragraph 9, and citations therein);

(4) Despite the need and related gonadotropin formulations being prepared with benzyl alcohol, FSH had not been so formulated for the 30 years it had been on the market (Declaration of Dr. Beals, paragraph 41);

(5) Protein-preservative compatibility is largely unpredictable. One skilled in the art would not have a reasonable expectation that any given preservative would be compatible with FSH (Declaration of Dr. DeFelippis, paragraphs 12-13);

(6) In view of the literature and product history, one skilled in the art would expect protein instability when formulating FSH with benzyl alcohol at the time of invention (Declarations of Dr. Beals, paragraph 69 and Dr. DeFelippis, paragraph 13);

(7) FSH formulated with benzyl alcohol unexpectedly maintained stability indicating that multi-use formulation was possible (Declaration of Dr. Wijayaratne);

(8) One skilled in the art would not interpret *Skrabanja* or *Andya* as suggesting the present invention or as providing a reasonable expectation of success (Declaration of Dr. DeFelippis, paragraphs 16-19);

(9) "General knowledge" in the field would not lead one skilled in the art to combine *Skrabanja* or *Andya* nor would it provide an expectation of success (Declaration of Dr. DeFelippis, paragraph 21); and

(10) Products comprising human FSH and benzyl alcohol in an aqueous diluent were commercially sold in 2001 and have been commercially successful. A significant distinction between these products and prior products is the use of stable solutions of FSH and benzyl alcohol that enable multi-use, solution products.

In view of this evidence, argument and the law, the rejection of Claim 128 is improper. Accordingly, Applicants request that the rejection be withdrawn so that the application can proceed to allowance without further delay.

Respectfully submitted,

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Eli Lilly and Company
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May 18, 2004

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date appearing below.

ELI LILLY AND COMPANY

By Paula K. Davis Date May 18, 2004

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	James Arthur Hoffmann and Jirong Lu	
Serial No.	:	09/928,198	
Filed	:	August 10, 2001	Group Art Unit: 1647
For	:	FSH FORMULATION	Examiner: R. DeBerry
Docket No.	:	X-12383N	

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael R. DeFelippis, hereby state and declare that:

Background

1. I hold the degree of Doctor of Philosophy in Biochemistry from the Ohio State University, and I am currently a Research Advisor at Eli Lilly and Company (Lilly), Indianapolis, Indiana. I have been a scientist with Lilly since 1990 and have been involved with formulation development for numerous protein products. I have authored or co-authored numerous peer-reviewed publications, book chapters, and review articles. I am an inventor or co-inventor on seven U.S. Patents. My *curriculum vitae* is attached.
2. I have read and understand the above referenced U.S. Patent Application Serial No. 09/928,198 ("'198 Application") and the current claims. I have also read and understand

the most recent Office Action for the '198 Application, mailed on March 18, 2004, as well as the references cited in the Office Action. These references include EP 0 853 945 by Skrabanja *et al.* ("Skrabanja"), U.S. Patent No. 6,267,958 by Andya *et al.* ("Andya"), and Keene *et al.* ("Keene"), *J. Biol. Chem.* 264(9):4769-75 (1989). I also reviewed the prior Office Actions, the references cited therein, and the Declarations filed therewith.

3. I understand that the '198 Application has an earliest effective filing date of July 23, 1998. This declaration describes the state of the art as I understood it while working as a formulation scientist on and before that date.

The Invention

4. The '198 Application is directed to a liquid formulation of follicle stimulating hormone (FSH) that is suitable as a multi-dose product. To be suitable as a multi-dose product, the formulation: 1) must meet the requirements for anti-microbial effectiveness (*i.e.,* microbiological stability), and 2) must be otherwise suitably stable prior to and during use (*i.e.,* chemical, physical, and conformational stability). I understand that the pending claims of the '198 Application are directed to human FSH and benzyl alcohol in an aqueous diluent, wherein (a) the concentration of FSH is 5.0 μg/mL to 2 mg/mL, (b) the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions, and (c) the formulation is suitable for multi-dose administration by injection.

5. The claimed formulation requires benzyl alcohol. Benzyl alcohol is recognized in the art as a "preservative." That is, it provides microbiological stability. I understand that two products are now commercially sold, PUREGON® brand FSH and GONAL-F® Multi-Dose brand FSH. Both products comprise human FSH and benzyl alcohol in an aqueous diluent as described by the claim.

Conformational and Physical Stability of Protein Formulations

6. The addition of a preservative, including benzyl alcohol, to some protein formulations has been shown to have a destabilizing effect on physical properties of the protein. For example, meta-cresol and benzyl alcohol are known to cause aggregation of some single-chain protein molecules. See, for example, Maa and Hsu, *Intl. J. Pharm.* 140:155-58 (1996), reference CBU on Applicants' Information Disclosure Form 1449; Lam *et al.*, *Pharm. Res.* 14(6):725-29 (1997); Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998),

reference CAC; Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997), reference CAB; and Akers, *J. Pharm. Sci.* 91(11):2283-2300 (2002), reference CCB.

7. Yet, in the preserved liquid formulation of the '198 Application, the FSH heterodimer exhibits comparable physical and conformational stability to an unpreserved control FSH solution that lacks benzyl alcohol. In my opinion, a person skilled in the art could not predict these results, nor would such a person have any expectations that such results could be achieved at the time of the effective filing date of the '198 Application.
8. For protein formulations, physical stability of the protein is one concern. Physical stability is a measure of undesirable aggregation of the protein: typically a decreased propensity towards aggregation is correlated with greater physical stability of the protein.
9. Another concern is conformational stability. FSH is a non-covalently bonded glycoprotein heterodimer comprised of an α-subunit and a ß-subunit. The quaternary structure of the heterodimer (*i.e.,* subunit association) results from weak interactions between the subunits known as non-covalent bonds. These include hydrophobic and electrostatic interactions, hydrogen bonding, and van der Waals forces. Because the interactions are relatively weak, non-covalent bonds are more easily disrupted than covalent bonds. For example, the non-covalent bonds between the α- and ß-subunits of FSH are weaker than the crosslinking covalent bonds between the A and B chains of insulin. If the quaternary structure of FSH is disrupted and the subunits dissociate, FSH becomes biologically inactive. Thus, FSH must be formulated such that the subunits maintain association. The ability to maintain the heterodimer structure is referred to as conformational stability.
10. Highly purified FSH was known to be conformationally unstable. (See, *inter alia*, Skrabanja, page 3, lines 51-54). This is especially true for relatively dilute aqueous solutions of FSH. *Id.* Because of this instability, FSH was stored as a lyophilized powder and reconstituted with solvent immediately before use.
11. The conformational stability of FSH, a non-covalently bonded heterodimer, when stored as a solution with a preservative such as benzyl alcohol, was not predictable from results achieved with other proteins.

12. Moreover, the effect of preservatives on the physical stability of FSH when stored in a solution with a preservative such as benzyl alcohol was not predictable from results achieved with other proteins.
13. In my opinion, an experienced formulator of therapeutic protein formulations would recognize that protein-preservative compatibility is dependent on the properties of the protein and preservative chosen. Therefore, compatibility is unpredictable without extensive experimentation. One cannot predict that any particular protein-preservative combination would be compatible, and thus lead to a stable formulation, merely because another protein demonstrated compatibility with that preservative. For example, although some proteins (*e.g.*, human chorionic gonadotropin and erythropoietin) have been shown to be stable over a one or two month period using benzyl alcohol as a preservative, others (e.g., interferon-γ, interleukin 1-R, and insulin-like growth factor 1) have been demonstrated to be physically unstable when preserved with benzyl alcohol (Lam *et al.*, *Pharm. Res.* 14(6):725-29 (1997); Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998); and Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997), respectively).
14. While conformational stability and physical stability cannot be predicted from the successes or failures of other proteins, the evidence available to an ordinarily skilled artisan at the time of the effective filing date of the '198 Application suggested that FSH would be unstable with many excipients, including benzyl alcohol. For example, FSH had known conformational instability (see Strickland and Puett, *Biol. Chem.* 257:2954-60 (1982), reference CAR; Reichert and Ramsey, *J. Biol. Chem.* 250:3034-40 (1975), reference CB); and products comprising FSH had a long history of being sold as lyophilized preparations to be reconstituted, used immediately, and the remainder discarded. From a formulation scientist's perspective, lyophilized single-dose vials would only be used for highly unstable proteins. Thus, having been sold in such a form for many years, it would have been reasonable to infer (particularly in view of the scientific literature and the heterodimer structure) that preserved, solution formulations were not stable. Accordingly, prior to the present invention, the data and circumstances suggested FSH would be unstable with preservatives, including benzyl alcohol.

The Art Cited by the Examiner

15. The cited art references collectively do not make the physical and conformational stability of the claimed formulation predictable, nor do the references provide any expectation of success.
16. Keene merely teaches the construction of vectors and the expression of human FSH using these vectors. This reference does not teach or even suggest any formulation containing FSH, especially not an FSH formulation preserved with benzyl alcohol.
17. Skrabanja teaches that a liquid formulation of FSH and citrate can be stabilized by the addition of a sufficient amount of a thioether, preferably methionine, to the formulation. This reference is quite complete, describing the required and optional excipients in detail. Skrabanja does not convey that a stable liquid formulation could be achieved by other means. Nor does it suggest that a preservative such as benzyl alcohol could or should be added to the FSH-containing composition.
18. Skrabanja makes reference to the Becton-Dickinson B-D pen injector. I am familiar with this device. Skrabanja also notes that "the liquid medicament can be in the form of a cartridge for multiple use." These passages are unclear. If Skrabanja intended these passages to imply the use of additional excipients such as a preservative, I find it implausible that Skrabanja is silent on preservatives, given the known issues of preservative compatibility, the known instability of the FSH heterodimer, and the criticality of preservatives to any multi-dose preserved formulation. Thus, one skilled in the art is unable to draw any conclusions from these passages.
19. Andya teaches a lyophilized protein formulation which can be reconstituted to generate a high concentration solution suitable for injection. FSH is one of an extensive list of possible proteins for use in such formulation. Benzyl alcohol is included in a similarly extensive list of possible excipients and is identified as a preferred preservative. However, in my opinion, one skilled in the art would not interpret this as a suggestion to use benzyl alcohol with all of the proteins listed. Several of the proteins listed were known to be incompatible with benzyl alcohol. (See paragraph 12, *supra*). Accordingly, this reference simply conveys to the ordinary skilled formulation scientist that benzyl alcohol would be a preferred preservative for those antibodies described and exemplified,

anti-HER2 and anti-IgE. This reference does not convey that the entire list of proteins could be stably formulated with benzyl alcohol.

20. Given that hundreds of proteins are listed in Andya (FSH is one in the list), a formulation scientist would understand that stability of the formulation would depend upon which protein, preservative, and other excipients were chosen, and that the stability would need to be determined through testing. Andya does not convey that all formulations containing a protein and a preservative would be pharmaceutically acceptable and stable.
21. Moreover, Andya's invention requires a very high protein concentration ($\geq$50 mg protein/mL diluent), whereas the claimed invention of the '198 Application requires a concentration of 5.0 μg/mL to 2 mg/mL. Thus, the protein concentrations in Andya are at least 25 times more concentrated, and perhaps even 10,000 times or more concentrated. As mentioned in paragraph 9 of this declaration, at the time of the effective filing date, relatively dilute solutions of FSH were known to be conformationally unstable (Skrabanja, page 2, 42-45). In my opinion, stability of Andya's extremely high concentrated protein solution does not predict or suggest stability of an FSH solution with a much lower concentration.
22. Thus, the cited art references collectively do not convey, suggest or motivate an ordinarily skilled formulation scientist to select benzyl alcohol from the list of excipients in the lyophilized formulation of Andya, and to add such to the liquid gonadotropin formulation of Skrabanja, having a human FSH sequence as taught by Keene, with any expectation of success that such a combination would yield a preserved FSH formulation that is as stable as an FSH formulation that does not contain such preservative.

Summary

23. In summary, physical and conformational stability of a liquid formulation of FSH in a preserved aqueous solution is not predictable from the cited references or the general state of the art. The stability of a non-covalently bonded FSH heterodimer in a preserved liquid formulation was not known in the art at the time of the effective filing date, nor did anything in the art suggest that FSH would remain stable in such a formulation. The data and circumstances surrounding FSH in 1998 would suggest that FSH may be unstable in the presence of a preservative and benzyl alcohol in particular. Thus, the stable formulation achieved in the '198 Application was unpredictable and unexpected.

24. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Michael R. DeFelippis, Ph.D.

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Education

B.S. 1985: Fairleigh Dickinson University, Teaneck, NJ
Major: Biochemistry

Ph.D. 1990: The Ohio State University, Columbus, OH
Major: Biochemistry
Academic Advisor: Michael H. Klapper, Ph.D.
Thesis: The Redox Potentials of the Tyrosine and Tryptophan Radicals and Long-Range Electron Transfer Between Tyrosine and Tryptophan in Peptides

Employment/Research Background

Research Advisor, Biopharmaceutical Product Research and Development, 2004-present: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Senior Research Scientist, Pharmaceutical Product Development, 2000-2004: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Research Scientist, Biopharmaceutical Product Development, 1996-1999: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Senior Pharmaceutical Chemist, Biopharmaceutical Product Development, 1990-1995: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Research Associate and Teaching Assistant, 1985-1990: The Ohio State University, Columbus, Ohio

Visiting Graduate Student Researcher, December, 1986-January, 1987: Ben Gurion University, Beer Sheva, Israel

Undergraduate Researcher, Summer 1985: Savannah River Ecology Laboratory, Aiken, South Carolina

Honors/Awards

President's Award, Lilly Research Laboratories (1994).

2500 Day Speed to Market Award (1994), Eli Lilly and Company Product Development.

First place, Albert L. Henne Research Competition, Department of Chemistry, The Ohio State University (1989).

Dean's Award, College of Science and Engineering, Fairleigh Dickinson University, 1985.

Professional Affiliations

American Chemical Society, 1985-present

Peer Reviewed Publications

Snavely, W.K., Subramaniam, B., Rajewski, R.A. and DeFelippis, M.R. (2002) "Micronization of Insulin from Halogenated Alcohol Solution Using Supercritical Carbon Dioxide as an Antisolvent". J. Pharm. Sci. 91, 2026-2039.

Yip, C.M., Brader, M.L., Frank, B.H., DeFelippis, M.R., and Ward, M.D. (2000) "Structural Studies of a Crystalline Insulin Analog Complex with Protamine by Atomic Force Microscopy", *Biophys. J.* 78, 466-473.

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Weinstein, M., Alfassi, Z.B., DeFelippis, M.R., Klapper, M.H., and Faraggi, M. (1991) "Long Range Electron Transfer Between Tyrosine and Tryptophan in Hen Egg-White Lysozyme", *Biochim. Biophys. Acta*, 1076, 173-178.

DeFelippis, M.R., Murthy, C.P., Broitman, F., Weinraub, D., Faraggi, M., and Klapper, M.H. (1991) "Electrochemical Properties of Tyrosine Phenoxy and Tryptophan Indolyl Radicals in Peptides and Amino Acid Analogues", *J. Phys. Chem.*, 95, 3416-3419.

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Invited Book Chapters and Review Articles

DeFelippis, M.R. (2003) "Overcoming the Challenges of Noninvasive Protein and Peptide Delivery". *Am. Pharmaceut. Rev.* 6, 21-30.

DeFelippis, M.R., Chance, R.E., and Frank, B.H. (2003) "Insulin Chemistry and Pharmacokinetics" in *Ellenberg & Rifkin's Diabetes Mellitus*, 6th Edition, Porte, Jr., D., Sherwin, R.S. and Baron, A. (Eds.) McGraw-Hill, New York, Chapter 28.

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DeFelippis, M.R., Chance, R.E., and Frank, B.H. (2001) "Insulin Self-Association and the Relationship to Pharmacokinetics and Pharmacodynamics", *Critical Reviews in Therapeutic Drug Carrier Systems*, 18(2), 201-264.

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Presentations and Meeting Abstracts

DeFelippis, M.R. (2003) "Comparability Assessment: Role of Formulation". Invited oral presentation at the PDA/IABS Conference on Comparability. Prague, Czech Republic, February 28.

DeFelippis, M.R. (2003) "Overcoming the Challenges of Noninvasive Protein and Preptide Delivery". Invited oral presentation at CBI's 6th Drug Delivery Conference, Philadelphia, PA, April 8.

DeFelippis, M.R. (2003) "Comparability Assessment: Role of Formulation". Invited oral presentation at the Health Canada Shared Learning Symposium. Toronto, Canada, November 18.

Khan, A. and DeFelippis, M.R. (2002) "How Technological Advances in Protein and Peptide Delivery Systems Ensure Commercial Success". Oral Presentation at CBI's 5th Drug Delivery Conference, Philadelphia, PA, April 8-9.

Dobbins, M.A., DeFelippis, M.R., Frank, B.H. and VanAntwerp, W. (2002) "Solution Formulation of Insulin Lispro with Increased Physical Stability for Pump Application". Poster presented at Formulation Strategies for Biopharmaceuticals Conference, Miami, FL, February 4-6.

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J.P. Richards, M.P. Stickelmeyer, S. Pye, M. Barbeau, J. Radziuk, B.H. Frank & M.R. DeFelippis. 1998. "Preparation and Characterization of a Microcrystalline Suspension Formulation of LysB28ProB29-Human Insulin", published abstract *Diabetes*, 47 (Supp. 1): A352.

J.P. Richards, M.R. DeFelippis, D.B. Flora, R.E. Chance, B.H. Frank B.H. & M.P. Stickelmeyer, M.P. 1997. "Association Properties of Monomeric Insulin Analogs Under Formulation Conditions". Poster Presented at the First Annual Beckman Symposium on Solution Interaction of Macromolecules, Galveston, Texas, November 14-17.

C.M. Yip, M.R. DeFelippis, M.R. Ward & M.L. Brader. 1997. "In Situ Determination of Molecular Packing and Growth Mechanisms in Protein Crystals: Atomic Force Microscopy of Insulin and Insulin Analogs". Lecture Presented at the American Crystallographic Association Annual Meeting, St. Louis, Missouri, July 19–25.

M.R. DeFelippis, C.M. Yip, M.D. Ward & M.L. Brader. 1997. "Structural Studies of an Insulin Analog Cocrystal Form by Atomic Force Microscopy". Lecture Presented at the American Crystallographic Association Annual Meeting, St. Louis, Missouri, July 19–25.

E. Ciszak, B.H. Frank, J.M. Beals, C.M. Yip, M.R. DeFelippis & G.D. Smith. 1997. "Structural Studies of Lispro-Insulins". Poster Presented at the American Crystallographic Association Annual Meeting, St. Louis, Missouri, July 19–25.

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M.R. DeFelippis. 1996. "Pharmaceutical Research and Development". Invited Lecture for a course on Clinical Drug Development: A Regulatory Review. Butler University, September 11th.

J.R. Radziuk, B. Bradley, L. Welsh, M.R. DeFelippis & P. Roach. 1996. "Neutral Protamine Lispro: Activity Profile of S.C. Administration with and without Admixture of Soluble Lispro". 32nd Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria, 1–5 September

M.R. DeFelippis, D.L. Bakaysa, K.M. Youngman, J. Radziuk & B.H. Frank. 1996. "Preparation and characterization of neutral protamine lispro (NPL) suspension". Diabetes 45 Suppl 2:74A. Abstract 267.

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